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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Ebrahim Zandi

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EXAMINER

PROUTY, REBECCA E

ART UNIT

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1652

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/079,949	Applicant(s) ZANDI ET AL.	
	Examiner Rebecca E. Prouty	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 July 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,5-7,17-19 and 21-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,5-7,17-19 and 21-23 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>7/08</u> . | 6) <input type="checkbox"/> Other: _____ |

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/17/08 has been entered.

Claims 1, 3, 4, 8-16, 20 and 24-41 have been canceled. Claims 2, 5-7, 17-19 and 21-23 are still at issue and are present for examination.

Applicants' arguments filed on 7/17/08, have been fully considered but are not deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

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Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 5-7, 17-19, and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Li et al. or Rothwarf et al. (Reference C27 of Applicant's PTO-1449) in view of Traincard et al. and Epinat et al.

Each of Li et al. and Rothwarf et al. teach the coexpression of IKK α , IKK β and IKK γ genes in a eukaryotic host by inserting the genes encoding each subunit fused to a tag (HA, FLAG or c-myc) into a mammalian expression vector, growing the host cell, lysing the host cell, and immunoprecipitating the IKK complexes. The only difference in the methods taught by Li et al. and Rothwarf et al. to the methods of the instant claims is that in the instant claims the expression host used is yeast.

Traincard et al. teach that within eukaryotic organisms, no homologs of any of member of the NF- κ B signaling system (clearly disclosed as including Rel/NF- κ B subunit genes, I κ B subunit genes and IKK genes) has been found within the genomes of *C. elegans* or *Saccharomyces cerevisiae* both of which were fully sequenced genomes at the time of publication of Traincard et al.

Epinat et al. teach that yeast is a convenient host for the reconstitution of the NF- κ B system since it does not contain any endogenous NF- κ B activity (see page 603) and that the reconstituted system provides an easy assay for testing stimuli or specific proteins that are postulated to be involved in NF- κ B signaling (see page 609). Epinat et al. further suggest that yeast lack any endogenous IKK activity (see Figure 4 and page 609) and teach expression vectors for the recombinant expression of genes involved in the NF- κ B signaling pathway in yeast cells under the control of both constitutive promoters such as the *ADH1* promoter and inducible promoters such as the *GAL1* promoter. The yeast expression vectors comprise selection markers such as the *URA3* or *LEU2* genes.

As the IKK complex is well known to be the part of the NF- κ B signaling pathway responsible for I κ B phosphorylation and as both Traincard et al. and Epinat et al. clearly suggest that yeast lack any endogenous IKK activity (as Traincard et al. teach that no IKK homologous genes were found in the yeast genome and Epinat et al. showed that an expressed I κ B protein could not be phosphorylated in yeast even under similar stimuli to those known to induce I κ B phosphorylation in mammals) and as yeast are well known in the art to be the workhorse organism for the expression of eukaryotic proteins of interest, it would have

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been obvious to one of ordinary skill in the art to reconstitute the IKK complex in a yeast host cells by expressing the IKK subunit genes of Li et al. or Rothwarf et al. in yeast using any known yeast expression vector or yeast expression vectors as taught by Epinat et al.

Applicants traversed the instant rejections by submitting an affidavit under 1.131 to swear behind the date of the Li et al. reference and submitting arguments regarding the rejection over Rothwarf et al. in view of Traincard et al. and Epinat et al. The affidavit filed on 7/17/08 under 37 CFR 1.131 has been considered but is ineffective to overcome the Li et al. reference because while the declaration states that Exhibit A shows a reduction to practice wherein the activity of a purified IKK complex from yeast transformed with either IKK β , IKK $\beta\gamma$, or IKK $\alpha\beta\gamma$ compared to mammalian IKK complex isolated from control Hela cells or TNF stimulated HELA cells was determined and that a substantially homogenous and biologically functional IKK protein complex was separated from the yeast, the declaration provides so little explanation of what the experiments of exhibit A show (i.e, what was done in each experiment and what does each gel shown comprise in each lane) that one cannot conclude that this is in fact shown. As such the rejection over

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Li et al. in view of Traincard et al. and Epinat et al. is maintained.

With regard to the rejection over Rothwarf et al. in view of Traincard et al. and Epinat et al., applicants argue that while Traincard et al. and Epinat et al. teach that no member of the NF-kappaB pathway exists in *Saccharomyces cerevisiae* and that yeast lacked the ability to phosphorylate the Ikb protein, that the art fails to teach or suggest the production of substantially homogenous and biologically functional IKK protein complex because Rothwarf et al. 1) does not teach the autophosphorylation of the IKK complex by the IKK γ subunit; 2) does teach that the mammalian IKK complex requires post-translational processing or "activation" by protein kinases to produce biologically functional IKK complex in mammalian cells and 3) does not teach that the active IKK complex produced in yeast could be produced by coexpression of either NIK or MEKK1

However, this is not persuasive because knowledge that the IKK complex is autophosphorylated by the IKK γ subunit would not have been necessary for an expectation of production of substantially homogenous and biologically functional IKK protein in yeast as a skilled artisan would clearly expect all inherent functions of the α , β , and γ subunits to be present when they are coexpressed in any eukaryotic system. Furthermore, Rothwarf

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et al. clearly teach the importance of phosphorylation of the IKK complex for its kinase activity, teach that unstimulated cells producing the IKK complex still have a basal level of kinase activity and further teach that the IKK complex can be phosphorylated *in vitro* by the NIK and MEKK1 proteins to produce an active complex. As such one of skill in the art would reasonably expect that coexpression of the three subunits together in yeast would produce a complex that would have the basal level of kinase activity demonstrated by the unstimulated cells of Rothwarf et al. and even if this in fact proved not to be the case a skilled artisan would have clearly expected that active complex could be produced by coexpression of either of NIK or MEKK1 in the yeast host as this is clearly taught by the art. As such the possible lack of knowledge that the IKK complex is autophosphorylated by the IKK γ subunit would not have prevented a skilled artisan from selecting yeast as a suitable host as the art clearly taught how to activate the complex if it was not active upon expression and coexpression of NIK or MEKK1 in the yeast is clearly not excluded from applicants claims. In response to this statement in the previous Office Action applicants submitted a declaration by Dr. Zandi which states that "Rothwarf et al., supra, on page 297, right column, lines 16 - 19, teaches that IKK- α/β can be phosphorylated and

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activated by overexpression of NIK and MEKK1 in mammalian cells, but does not teach that the IKK complex from yeast of the present application containing IKK α , IKK β , and IKK γ can be activated by NIK or MEKK1 in yeast systems. Rothwarf et al. also teaches that the physiological role of NIK and MEKK1 in IKK activation by pro-inflammatory cytokines is not clear."

However, this statement is insufficient to overcome the explicit teaching by Rothwarf et al. that overexpression of NIK and MEKK1 can be used for activation of the IKK complex. It is not necessary for a skilled artisan to have an expectation that these are the physiological activators, merely that the overexpression of them provides the necessary activation of the complex. The declaration provides no reason for believing that overexpressing NIK or MEKK1 wouldn't have the same effect on the IKK complex in yeast cells that it has in mammalian cells. As such the rejection is maintained.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rebecca E. Prouty whose telephone number is 571-272-0937. The examiner can normally be reached on Tuesday-Friday from 8 AM to 5 PM. The examiner can also be reached on alternate Mondays

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat Nashed, can be reached at (571) 272-0934. The fax phone number for this Group is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval

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(PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Rebecca Prouty/
Primary Examiner
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